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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 10/807,034 | 03/18/2004 | Terence G. Oas | 180/1172/2 DIV | 2899 |
| 25297 | 7590 | 01/10/2006 | EXAMINER | |
| JENKINS, WILSON & TAYLOR, P. A. 3100 TOWER BLVD SUITE 1400 DURHAM, NC 27707 | | | CHEU, CHANGHWA J | |
| | | ART UNIT | PAPER NUMBER | 1641 |

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/807,034 | OAS ET AL. | |
| | Examiner | Art Unit | |
| | Jacob Cheu | 1641 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 04 November 2005.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 23-124 is/are pending in the application.
- 4a) Of the above claim(s) 41-124 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 23-40 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>7/19/04; 2/1005</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election of group I, claims 23-40 in the reply filed on 11/4/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election *without traverse* (MPEP § 818.03(a)).

Currently, claims 23-40 are under examination. Claims 41-124 are withdrawn from further consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 38, step (c), it is not clear what applicant means "change in the position". Figure 15, Figure 19-20, demonstrate the protein/ligand interaction, it is not clear what "position" change in these Figures, or alternatively, applicant means the shape/or curve change in response to the presence of ligand. Applicant needs to clarify.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claim 23-36, 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rogona et al. (applicant's submitted IDS on 2/10/2005, reference #5; J Molecular Biology 1999 Vol. 293, page 953) in view of Smith et al. (Biochemistry 1998 Vol. 63, page 285) in combination with Ehring et al. (Analytical Biochem 1999 Vol. 267, page 252).

Ragona et al. teach a method of studying protein stability. Ragona et al. teach using buffer solution containing hydrogen/deuterium exchange method (i.e. $^2\text{H}_2\text{O}$) and varying denaturant (i.e. urea, ranging from 0-7 M) in NMR to quantitatively study the protein stability, e.g. unfolding and refolding. (See Abstract and page 966, Materials and Methods- NMR measurement; equations (3) and (8)). However, Ragona et al. do not teach (1) a binding event, e.g. ligand bound to a protein; (2) using mass spectrometry (MS) for analysis.

Smith et al. teach using MS analysis coupling with hydrogen/deuterium exchange method to study protein folding/unfolding stability. Smith et al. disclose the advantages of using MS over NMR analysis because MS permits studies of large proteins, require only picomoles of protein, and provides a direct measure of structural heterogeneity (See Abstract, last portion).

Ehring et al. teach using similar MS analysis coupling with hydrogen/deuterium exchange method to study protein interaction for important biological/physiological functions and processes, e.g. ligand bound to the protein, such as insulin-like growth factor I and its binding protein (See Abstract; page 252, left column, last paragraph to first paragraph of right column).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to have motivated Rogona et al. to adopt MS analysis as taught by Smith et al. to study protein/ligand interaction as taught by Ehring et al. with reasonable expectation of success because MS provides advantages superior than NMR, and protein/ligand interaction is an important biological process well-known and often studies in the field.

With respect to claim 24-25, Ehring et al. isolated and purified the insulin-like growth factor I and the related binding protein (See Materials, page 253, right column, “provided in-house”).

With respect to claim 27-28, Ragona et al. use a dimer bovine beta-lactoglobulin, molecular weight is 36 kDa (less than 1000 kDa) as the test protein (page 954, first paragraph)

With respect to claim 32-33, Smith et al. teach that the amount of test protein can be of small amount, such as picomolar (See Abstract).

With respect to claim 34-35, Ragona et al. teach varying denaturant, i.e. urea, concentration for analysis of the exchange of hydrogen/deuterium (See method and material, equation (3) and (8)).

With respect to claim 36, Smith et al. teach using MALDI mass spectrometry for analysis (See Abstract).

With respect to claim 38, it would have been obvious to see the difference, e.g change in shape or curve as the function of denaturant (urea) with the change of mass under MALDI analysis between the interaction of protein/ligand (presence of ligand) versus protein only (absence of ligand). One ordinary skill in the art would have tested both conditions, i.e. presence and absence of ligand, because it is a routine practice to test control condition (without ligand) compared with the variable, i.e. presence of ligand.

With respect to claim 40, Ragona et al. conduct the experiment using reference protein, e.g. non-denaturant protein as the control. (Figures 4)

7. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ragona et al. in view of Smith in combination with Ehring et al., and further in view of Villanueva et al. (applicant's submitted IDS, reference #6; Fed. Euro. Biochem Soc 2000 Vol. 472, page 27).

Ragona, Smith and Ehring et al. references have been discussed but do not explicitly teach using sinapinic acid for MALDI mass spectrometry.

Villanueva et al. teach treat the mass matrix material with sinapic acid. (page 28, Section 2.6 Preparation of samples for MALDI-TOF MS).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to have provided Ragona, Smith and Ehring et al. with the packing material for MALDI, such as sinapinic acid as taught by Villanueva et al. because it is well-known and widely practice in the art by using this material for MADLI.

Conclusion

8. No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner



Art Unit 1641

December 26, 2005

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600


01/04/06